

Mr. P. O. Fern.

Serum Protein Abnormalities and Disorders of the Gut

Introduction

Serum protein deficiencies may occur secondary to protein losing enteropathy. The majority of the disorders responsible for protein losing enteropathy are located in the small intestine, a proportion in the stomach, and ulcerative colitis is the only common disease of the large intestine causing significant protein loss. Examples of such disorders include gastrointesrinal amyloidosis, blind-loop syndromes, Crohn's disease, intestinal lymphangiectasia, radiation, some inflammatory disorders and idiopathic steatorrhoea. In most of these diseases, whatever their origin, some common features can be recognised : serum albumen is consistently low and chronic oedema the rule. The hypoproteinaemia is hypercatabolic i.e. due to increased breakdown (in the gut) with loss into the intestinal lumen and insufficient compensatory increased production.

Recently another association has been recognised, that of gut abnormalities and primary serum gammaglobulin disorders ; a 'sprue-like' syndrome is said to occur in 20% of patients with primary acquired hypogammaglobulinaemia² and a specific deficiency of immunoglobulin A (IgA) has been reported in several cases associated with malabsorptive disease.³ It is likely in these patients that the immunoglobulin deficiency is the primary event and not due to the state of malnutrition following malabsorption.

Four cases are presented three of which have an immunological



deficiency, which, it is argued, is primary and these are contrasted with the more common association of serum protein abnormality secondary to disease of the bowel.

CASE 1.

Diagnosis : 1. Primary acquired hypogammaglobulinaemia.
2. Malabsorption.

History :

This 60 year old clerk was first seen at the Northern General Hospital in December 1958 with a history of repeated chest infections, with cough and purulent sputum since he was seventeen.

Past Medical History :

1927 Severe pneumonia following influenza.
1935 Right sided pleurisy
1936 Right sided pleurisy.
1940 Left sided pleurisy, pleural opacities at left base with collapse of right lower lobe.
1943 Pneumonia and pleurisy.
1945 Experienced his first episode of looseness of stools and was admitted to hospital where ^{it} ~~he~~ was decided that his symptoms were nervous in origin. He had an ischiorectal abscess drained.
1947 Pneumonia and pleurisy.
1947-50 Repeated exacerbations of his chest symptoms.
1950 Right sided renal colic with stone passed.
1950-56 Remained relatively well apart from exacerbation of his chest symptoms. Was seen at the Northern General Hospital during

an episode and his sputum was found to contain *Pneumococci* and *Proteus*. He was treated successfully with tetracycline.

- 1957 Bronchiectasis of the apical and posterior segments of the right upper lobe diagnosed. His stools had again become loose and now bulky. This settled when the tetracycline was stopped.
- 1958 Two acute exacerbations of chest symptoms, was admitted to N.G.H. on account of a complaint of retrosternal discomfort on exercise. He was investigated with the following findings :-

Investigations :

Haematology

1. Hb. 10.5g/100 ml with evidence of iron deficiency.
2. Reticulocytes <1%.
3. W.B.C. 8,000 with normal differential.
4. E.S.R. 1mm in the first hour.
5. Prothrombin activity : 61% of control.
6. Marrow biopsy : normoblastic.

Gastrointestinal function

1. Barium meal and follow through normal ; Barium enema normal.
2. Histamine fast achlorhydria.
3. Folic acid absorption test : normal.
4. Glucose tolerance test : normal.

5. Stool fat content on a diet containing approx.

100 g. of fat daily on four separate collections.

16.g./day

4.g/day

7.g/day

14.g/day

6. Serum Calcium : normal.

7. Serum albumen : normal.

Urine

1. Microscopic haematuria

2. Intravenous pyelogram showed a calculus in the lower pole of the left kidney.

3. Mid-stream urine culture : no growth.

Sputum

Pneumococci, Haemophilus influenzae.

Progress

His chest symptoms cleared with tetracycline and his anaemia responded to iron.

1959

He was investigated again for renal symptoms and cystoscopy and retrograde pyelography confirmed the presence of a stone in the lower calyx of the left kidney, but he was having no symptoms. At this time he was having four bulky stools per day which were difficult to flush. His stool fat excretion was again raised and there was no improvement when tetracycline was withdrawn. He was treated with a low fat, gluten free diet and his stools returned to normal. He remained well.

1963

On routine electrophoresis it was found that he was hypogammaglobulinaemic.

IgG : 120 mg/100 ml.

IgM : 25% of standard normal serum.

IgA : Absent.

Blood group O Rhesus Positive.

No. A, A₂ or B ischaemagglutinins.

Direct Coombs : negative.

Since 1963 his chest symptoms have been controlled with tetracycline and his bowels have remained normal. It was thought unnecessary to give replacement therapy with gammaglobulin. Regular estimations of his immunoglobulins since 1963 have shown no significant change.

Comment :

1. This is a case of primary immunological deficiency as a result of which the patient has had frequent chest infections.
2. Although the bowel symptoms resolved on withdrawal of tetracycline on one occasion, subsequently they persisted and steatorrhoea was proved. Other absorption tests and intestinal biopsy have not been performed.
3. The patients blood group was 'O' and no anti A or B ischaemagglutinins were detected, this is in keeping with hypogammaglobulinaemia.

Conclusion

This is an example of steatorrhoea in association with immunoglobulin deficiency.

Case 2Diagnosis

1. Peptic ulcer.
2. Gluten sensitive enteropathy.
- (3. IgA absent)

History

1965 - This 26 year-old man was admitted to the Royal Infirmary for intensive treatment of a duodenal ulcer and for assessment for surgery. He gave a three year history of episodes of epigastric pain with all the clinical features of peptic ulceration ; the symptoms had become more frequent and the pain more severe over the few months just prior to admission and in spite of strict adherence to a medical peptic ulcer regime he had lost 12 Kg. weight over the past three years. He had been passing one to two normal sized motions per day which were well formed and of normal dark colour ; however from childhood there were episodes during which he had frequent bulky motions which tended to float. Blood and mucus were never present.

On examination the patient was thin but not emaciated ; was 5'6" in height and his weight was 56.3 Kg. He was of normal adult development; no lymphadenopathy was found. There was slight tenderness in the left iliac fossa on palpation ; no masses or organs were palpable.

Investigations

- 1.. Haematology : (1) Hb. : 15.9g/100 ml.
- (2) P.C.V. : 48%
- (3) W.B.C. : 5,900/mm³ with normal differential.
- (4) E.S.R. : 1mm in 1st hour.

- (v) Serum B₁₂ : 509 µg/ml.
- (vi) Serum folate : 5.6 µg/ml.

2. Small bowel function

- (i) Faecal fat excretion on a diet containing approximately 100 g. fat daily was 7.5g/day on two five-day collections.
- (ii) D-Xylose absorption gave a 5 hour urinary excretion of 4.2g following an oral dose of 25g.
- (iii) Glucose tolerance test gave a fasting blood sugar level of 61 mg/100 ml and half-hourly values of 65, 65, 60 and 58 mg/100 ml. following an oral dose of 50 g. of glucose.
- (iv) Schilling test gave a urinary recovery of 18% in 24 hours.
- (v) Folic acid absorption showed a 24 hour urinary excretion of 5 mg of folic acid following a subcutaneous injection of 5 mg folic acid, and 3.4 mg after an oral dose of 5 mg (In the absence of small intestine disease at least 1.5 mg of folic acid should be excreted after and oral dose of 5 mg).

3. Pancreatic function tests : Within normal range.

4. Miscellaneous tests :

- (i) Blood urea and electrolytes : normal
- (ii) Urinalyses : normal.
- (iii) Liver function tests : normal.

- (iv) Protein bound iodine : normal.
- (v) Chest X-ray : normal.
- (iv) Plasma proteins : 6.5g/100 ml.
 - Albumen : 4.3g/100 ml.
 - α_1 : 0.3g/100 ml.
 - α_2 : 0.6g/100 ml.
 - β : 0.6g/100 ml.
 - γ : 0.8g/100 ml.
- (vii) Calcium : normal.
- (viii) Phosphate : normal.
- (ix) Alkaline phosphatase : normal.
- (x) 5 - hydroxyindole acetic acid urinary excretion : normal.
- (xi) Barium-meal demonstrated unequivocally a duodenal ulcer ; follow-through showed rather a rapid passage of barium through the small intestine but no other abnormality.
- (xii) Multiple biopsies taken about 6" from the duodeno-jejunal flexure by Crosby capsule under radiological control showed a flat mucosal surface under the dissecting microscope. The absence of villi was confirmed by light microscopy. Some abnormal epithelial cells and chronic inflammatory exudate were present.

Therapy

He was then given a gluten free diet alone ; this was followed by complete disappearance of symptoms within one week, though stools still tended to float on occasions. He gained weight.

Progress

Nine months after starting his gluten-free diet barium examination failed to show any duodenal ulcer ; Faecal fat excretion on a diet containing approximately 100 g. fat per day was 5.7 g. per day and 2.7g. per day on two successive collections. Jejunal biopsy from the same site as previously showed ridges and leaves and the dissecting microscope and light microscope revealed the presence of stunted villi and more normal epithelial cells. He remained well and 18 months after starting his gluten-free diet a challenge was carried out by giving the patient 40 g. of gluten per day ; faecal fat was estimated on a 5 day collection while he was on a diet containing approximately 100 g. of fat daily, both before and after the challenge with gluten : before gluten 6.2g /day and after gluten 10 g/day. Jejunal biopsy showed virtually absent villi after challenge also abnormal epithelial cells. Apart from two loose stools per day the patient did not complain of any symptoms. He has been followed up at regular intervals over the past four years and there has been some recurrence of ulcer symptoms on a ward diet. His weight has remained steady at 56 Kg.

Immunoglobulins. In May 1969 it was decided to assay this patient's immunoglobulins quantitatively and IgA was found to be totally absent ; IgG and IgM were normal.

Comment

1. This patient had symptoms of duodenal ulcer which only resolved when a gluten-free diet was given ; after this the ulcer healed.

2. Subtotal villous atrophy is demonstrated with minimal malabsorption. This state of affairs has been shown to exist in some other patients with malabsorption, for example the occasional patient may present with iron deficiency alone.

3. Immunological deficiency has been demonstrated. IgA is totally absent. This has been reported in one in five hundred ($1/500$) of the normal population⁴. The significance in relation to malabsorption is not known ; however IgA is probably the main immunological defence mechanism in the gut.

Case 3Diagnosis

1. Primary acquired hypogammaglobulinaemia
2. Pernicious anaemia.

History

1962. This 34 year old painter was first seen in the Royal Infirmary at the age of 27 in 1962 because of weight loss ; no cause was found and he was next seen in 1967 complaining of a sore tongue. He was admitted and fully investigated. On careful history taking it was found that he had had a five year history of intermittent frequent chest infections with purulent sputum and pleurisy and a six week history of numbness in the legs commencing in the toes, which interfered with his driving. He also complained of diarrhoea starting six weeks prior to the onset of his neuropathy, with three to four loose stools per day and a weight loss of 6 Kg in three months. He also had severe aphthous ulceration of the mouth. Prior to the onset of the chest infections at the age of 27 this man had been perfectly fit. There was nothing of note in his family history.

On examination there was no lymphadenopathy and no organs were palpable in the abdomen. Response to light touch and pin-prick sensation was diminished below the knee in both legs, the subjective sensation of numbness in both legs extended to the groin and he was having difficulty with walking.

Investigations1. Haematology

- (i) Hb. : 11.1g/100 ml.
- (ii) PCV : 37%
- (iii) W.B.C. : 5,200 with normal differential.
- (iv) Reticulocytes : < 1%
- (v) E.S.R. : 31mm in the first hour.
- (vi) Bone marrow : Cellular and normoblastic, abundant iron was present.
- (vii) Serum B₁₂ : < 50µg/ml.
- (viii) Serum folate : 23.4 µg/ml.

2. Small bowel function

- (i) D-xylose excretion 4.3g recovered in the urine following an oral dose of 25 g.
- (ii) Glucose tolerance test following oral dose of 50 g. glucose : normal.
- (iii) Faecal fat excretion was 3.8g/day and 2.9g/day on two separate collections on a diet containing approximately 100 g. of fat per day.
- (iv) Barium meal and follow-through revealed no abnormality.
- (v) Schilling test : 14% of 0.25 µg of ⁵⁷Co B₁₂ given orally, was shown to be retained for 7 days by whole body count method. (This result shows gross malabsorption)
- (vi) FIGLU test : normal.
- (vii) Folic acid absorption : recovery in the urine was 2.96 mg. following 5mg. subcutaneously and 1.98 mg. following oral administration of 5 mg.
- (viii) Jejunal biopsy by Crosby capsule under radiological control examined under the dissecting microscope revealed partial villous atrophy and histology showed heavy infiltration

of the lamina propria by lymphocytes, some germinal centres were present.

3. Maximal acid output was nil, with gastric juice pH 7.6.

Gastric juice intrinsic factor was 75 ng units which is in the pernicious anaemia range.

4. Miscellaneous tests

- (i) Blood urea and electrolytes : normal.
- (ii) Liver function tests : normal.
- (iii) Serum calcium : normal.
- (iv) Serum phosphate : normal.
- (v) Serum iron : normal.
- (vi) Total iron-binding capacity : normal.
- (vii) Uric acid : normal.
- (viii) Protein bound iodine : normal.
- (ix) I^{131} four-hour uptake : normal.
- (x) Chest x-ray showed old TB calcification.
- (xi) Mantoux : negative at $1/1000$, weakly positive at $1/100$.
- (xii) Kveim test : negative.
- (xiii) Pneumomediastinography showed a small thymus but within normal limits.
- (xiv) Serial stool culture : negative.
- (xv) Faecal occult blood : repeatedly negative.
- (xvi) Blood culture : repeatedly negative.
- (xvii) Mid stream urine culture : repeatedly negative.
- (xviii) Urinary excretion of 5. hydroxyindole acetic acid - normal.
- (xix) Total serum protein : 4.9g/100ml.

albumen	2.7 g/100 ml.
α_1 :	0.4 g/100 ml.
α_2 :	1.0 g/100 ml.
β :	0.6 g/100 ml.
γ :	0.2 g/100 ml.
- (xx) Direct and indirect Coombs : negative.

- (xxi) Anti-A and Anti-B isoagglutinins only just detectable.
Blood group O Rh. positive.
- (xxii) L.E. cells : negative.
- (xxiii) Immunoelectrophoresis showed : IgG : 42 mg/100 ml.
IgA : 2.5% of standard normal serum.
IgM : < 2.5% of standard normal serum.
- (xxiv) Intrinsic factor antibodies : absent.
- (xxv) Parietal cell antibodies : absent.

Progress :

During his stay in hospital a further chest infection with *Pneumococcus* and *Haemophilus influenzae* was treated. A 5% reticulocyte response followed treatment with vitamin B₁₂. The peripheral neuropathy remained at the level of the greater trochanter, and the patient's weight remained steady at 59 Kg. He was discharged on parenteral cyanocobalamin. He was followed up at regular intervals, gained weight and remained well.

Family studies During 1967 the other members of the patient's family were investigated for deficiency of immunoglobulins but all were found to be within the normal range.

Since the patient remained well it was decided to withhold gamma-globulin replacement therapy, but it was considered worthwhile to try a course of steroids in an attempt to improve immunoglobulin levels and gastric acid output, and he was also started on Multivite since his neuropathy had not cleared. However, 16 months of steroid therapy showed no alteration in the serum levels of immunoglobulin or gastric

acid so the treatment was tailed off and stopped in July 1969. He continued to remain well apart from intermittent mild chest infections, his bowels were normal and he gained weight.

Comments

1. This is a further case of primary immunological disease - gammaglobulin is virtually absent but with associated pernicious anaemia. This is a recognised association in which pernicious anaemia occurs early in life and there are no parietal cells or intrinsic factor antibodies in contrast with pernicious anaemia in the elderly when 96% of cases have parietal cell and intrinsic factor antibodies.⁵
2. As a result of absent immunoglobulins this patient has had numerous chest infections and infections of the alimentary tract.
3. The patient's blood group was "O", the fact that anti-A and anti-B isoagglutinins were barely detectable is in keeping with hypogammaglobulinaemia.

Conclusion

This is another example of alimentary disease secondary to immunological disorder and it is possible that this patient also had malabsorption at the stage when he had marked weight loss and diarrhoea prior to investigation. Certainly this had been shown to occur in other patients.

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Case 4

Diagnosis

1. Protein-losing enteropathy
2. Angioneurotic oedema
3. Chronic glomerulonephritis

History

This 60-year old labourer was admitted to hospital in October 1960 for investigation of recurrent and disabling oedema of the lower limbs of seven month's duration. For two years he had also suffered from attacks of urticaria, angioneurotic oedema and several attacks, lasting two to three days, of anorexia, colicky lower abdominal pain with profuse watery brown stools without blood or mucus. Stool cultures were repeatedly negative on these occasions as were tests for faecal occult blood ; these attacks subsided spontaneously.

Post medical history

Feb. 1960. He had been admitted to the Royal Infirmary following the finding of positive Wasserman and Kahn tests when blood had been taken off at the General Practice Teaching Unit during an attack of urticaria and oedema. The Treponema pallidum immobilisation test was also positive although there was no clinical evidence of syphilis. The C.S.F. showed no abnormality and he received a full course of penicillin therapy. He had had two previous admissions to hospital for treatment of his lower limb oedema which resolved with bed rest and antihistamines. There was no previous history or family history

of other allergic disease and no history of dietary neglect.

On examination he was moderately obese, weight 94 Kg ; height 180 cm ; and had gross pitting oedema of both lower limbs, the right side being worse than the left. The oedema extended to the knees ; he also had slight pitting oedema of the dorsum of the hands and puffy eyelids. Urticarial weals were present on the skin of his trunk. Examination of the cardiovascular and respiratory systems and of the abdomen were negative.

Investigations

1. Haematology

- (i) Hb. 12.6g/100ml.
- (ii) W.B.C. and differentail : normal.
- (iii) E.S.R. 9mm in the 1st hour.
- (iv) Bone marrow : normoblastic.
- (v) L.E. cells on four examinations were negative.

2. Small bowel function

- (i) D-xylose excretion)
- (ii) Schilling test) Normal results.
- (iii) Folic acid absorption)
- (iv) Jejunal biopsy by Crosby capsule : some oedema of the villi with moderate chronic inflammatory cell infiltration of the mucosae and muscularis mucosae.

3. Radiology

- (i) Chest x-ray : normal
- (ii) Inferior venocavogram and angiocardigram. Patent wide inferior vena cava with evidence of good flow : there was no evidence of any delay in pulmonary circulation and no evidence of pericarditis

- (iii) Intravenous pyelogram : Both kidneys moderately enlarged.
- (iv) Barium enema : normal.
- (v) Barium meal : Coursening of mucosal pattern of the stomach.

4. E.C.G. : normal.

5. Biopsies

- (i) Kidney Mixed proliferative and membranous glomerulonephritis with additional features of polymorph, neutrophil and eosinophil infiltration of the stroma.
- (ii) Liver No evidence of cirrhosis but liver cells and their nuclei varied considerably in size, some cells being binucleate, others having pyknotic nuclei and a few cells containing fatty vacoules.
- (iii) Pelvic colon : normal.

6. Miscellaneous tests

- (i) Total serum protein : 4.7 g/100 ml.
 albumen 2.1 g/100 ml.
 α_1 -globulin 0.3 g/100 ml.
 α_2 -globulin 0.7 g/100 ml.
 β -globulin 0.5 g/100 ml.
 γ -globulin 1.1 g/100 ml.
- (ii) Creatinine Clearance : 103 ml/min.
- (iii) Blood urea nitrogen : 17 mg/100 ml.
- (iv) Electrolytes : normal.
- (v) Serum cholesterol : 200 mg/100 ml.
- (vi) Liver function tests including B.S.P. retention : normal.

- (vii) Augmented histamine test : 12 mEq of hydrochloric acid in post-histamine hour.
- (viii) Gastroscopy : no significant abnormality.
- (x) Sigmoidoscopy to 20 cm. normal except for one small hyperplastic area of rectal mucosa.

Initially the hypoproteinaemia was thought to be due to urinary protein loss and since this averaged only 2.0 g/day it was assumed that this had been higher prior to investigation, and the investigations detailed revealed no other satisfactory explanation. The patient was discharged on the following therapeutic regime :

- (i) High protein diet
- (ii) Prednisolone
- (iii) Antihistamines
- (iv) Diuretics

Progress

After three months on this regime no significant change had occurred. All drugs were withdrawn and further investigations were started six months later to elucidate the cause of the hypoproteinaemia. The results obtained over three years of electrophoretic analysis of serum are presented in Table 1.

Electrophoretic analysis of serum over 3 yrs.

SERUM PROTEIN g/100 ml.	Total	Albumin	α_1	α_2	β	δ
MEAN	4.7	2.1	0.3	0.7	0.5	1.1
RANGE	3.6-6.2	1.2-3.2	0.2-0.6	0.4-0.9	0.3-0.8	0.7-1.9
Number of Estimations	26	26	19	19	19	19
Normal	5.6-8.0	3.3-4.6	0.1-0.4	0.5-1.0	0.6-1.1	0.6-1.2

An attempt was made then to estimate intestinal loss of albumin using the I^{131} - labelled albumin tumour study method of Cohen et alia with the modification of Jeejeebhoy and Coghill (14). The results obtained showed:

- (i) evidence of intestinal loss of albumin.
- (ii) a reduced albumin half-life (11 days).
- (iii) an increased fractional turnover rate (15% of the intravascular pool per day).
- (iv) a normal absolute turnover rate (11 G/day).

Despite the negative results of the gastrointestinal investigations and since the oedema remained refractory to treatment it was thought necessary to carry out laparotomy to exclude an undetected alimentary lesion amenable to surgery.

Laparotomy 1961. The upper half of the jejunum was swollen and oedematous and showed congestion of the subserosal vessels; the remainder of the small intestinal appeared healthy, and no abnormalities were detected on inspection and palpation of the stomach, duodenum, colon, liver, gall-bladder, pancreas or mesentery. Biopsies of the jejunum showed the oedema to be most marked in the submucosa and in this layer and in other main muscle coat there were collections of polymorph leucocytes including many eosinophils.

Treatment and progress.

Control of the hypoprotinaemic oedema was achieved by intravenous infusions of concentrated plasma proteins given at 3-4 monthly intervals. Occasional attacks of angioneurotic oedema and /

and intestinal colic continued to occur for some months but appeared to resolve spontaneously during 1963-64.

History since 1962. The patient developed severe glaucoma of the right eye secondary to iridocyclitis late in 1962, and had the left eye enucleated as a result of this.

A long history of exertional dyspnoea and paroxysmal nocturnal dyspnoea began in 1962 for which he was fully investigated in 1966 and again in early 1969; electrocardiography, cardiac angiography and full respiratory function tests failed to reveal any cause for the dyspnoea. In March 1969 he was admitted to the Coronary Care Unit with symptoms of myocardial infarction but E.C.G. and enzyme analysis failed to confirm the diagnosis. He was discharged home on Digoxin but continued to have exertional dyspnoea which prevented him from working from March to July 1969. Full respiratory function tests were repeated in July 1969 and a lung biopsy was carried out which showed mild emphysema but no other abnormality; lung scan, pulmonary angiography and cardiac catheterisation also failed to reveal any abnormality.

He has had no recent recurrence of angioneurotic oedema, bowel symptoms or urticaria and his serum proteins remain normal. Immunoglobulins were assayed in December 1969 and were within normal limits.

Comment.

1. This is a case of proven protein-losing enteropathy in which hypoproteinaemia with hypoalbuminaemia have been demonstrated over a three year period in which total protein averaged 4.7 G/100 ml. with/

with albumin 2.1 G/100 ml. and γ -globulin 1.1 G/100 ml. Intestinal loss of albumin was proven by I^{131} -labelled albumin tumour studies.

2. Many causes of protein-losing enteropathy exist, for example, 'blind-loop' syndromes, gastrointestinal amyloidosis and intestinal lymphangiectasia, but this case appears to have an allergic basis.

3. The protein loss was sufficient to give serum albumin of 1.2 G/100 ml. Yet the lowest γ -globulin was 0.7 G/100 ml., i.e. the latter are larger molecules, therefore since complete γ -globulin deficiency does not occur secondary to protein loss, the cases 1 - 3 are likely to be primary protein abnormalities; indeed measurement of IgG, A, M now shows no abnormality.

4. In spite of exhaustive investigations the cause of this patient's breathlessness has not been elucidated. It is likely that a combination of minimal left ventricular failure, a small degree of emphysema, considerable refractory obesity and depressed state of mind are the causal factors.

DISCUSSION1. The Immunoglobulins.

In 1959 the term 'immunoglobulin' was proposed for those globulins primarily associated with the lymphoreticular system, and until the W.H.O. publication in 1964 there existed some confusion as to the nomenclature of these proteins. The whole molecules are referred to as IgG, IgM, and IgA. IgG replaces the old terminology γ , 7S γ , and γ_2 ; IgM replaces γ_1^M , β_2^M ; IgA replace β_2^A , and γ_1^A . IgD and IgE, globulins with molecular weights of approximately 150,000 and 200,000 respectively have also been detected in serum but do not form part of this discussion.

IgG is a globulin of molecular weight approximately 150,000, consisting of four polypeptide chains, two large and two small linked by disulphide bridges. These light chains are common to all the principal groups of immunoglobulins and it is the characteristics of the heavy chains which differentiates IgG, M, A, D and E from each other. IgM exists in serum as a pentamer of five monomers linked by covalent bonds, the molecular weight is in the region of 900,000. The monomer IgA has a molecular weight of about 160,000, but it may sediment out in a heterogenous fashion as 7S, 11S, 13S and 15S components.

The immunoglobulins are produced in cells of the lymphoreticular system, and their production and release into the vascular compartment in response to antigenic stimulation is associated with an increase in the population of plasma cells in the bone marrow and lymph glands. In the normal adult, 50% of the free IgG is concentrated in the vascular space; about 5% of this is /

is catabolised daily. IgM is localised almost entirely in the vascular space, its rate of loss being about 15% daily. IgM is particularly well adapted to the handling of bacteria and other particulate antigens. IgG may be more effective in dealing with antigens in solution at the molecular level. IgA is distributed in approximately the same proportions as IgG but the loss from the vascular space per day is about 15%. IgA in external secretions is peculiar in that it has unique chemical as well as antigenic properties which are conferred upon it by the presence of a non-immunoglobulin glycoprotein called the secretory piece. External secretions which bathe mucus membranes in direct contact with the external environment, the tears, saliva, bronchial and gastrointestinal secretions show a predominance of IgA, which exists in these secretions in concentrations higher than those of plasma. Recent evidence suggests that these antibodies are produced locally by the plasma cells in the lamina propria of the gastrointestinal and respiratory tracts, and interstitially between salivary gland acini. The significance of the secretory piece has not clearly been established though it appears to render the IgA molecule more resistant to proteolytic enzymes. There is no evidence for or against its involvement in the transport of IgA from serum to the secretions. In Case 2 we have a selective deficiency of IgA, the biological significance of the secretory system of immunoglobulins in terms of its role in normal defences is at present under active investigation, but it seems likely that it has an important part in the regulation of the normal flora and resistance of the mucosal surfaces to colonisation by pathogenic organisms. It/

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It should be pointed out however, that although emphasis has been placed on the probable importance of IgA, because of its high concentration in external secretions, the role of the other immunoglobulins in these secretions is still quite unknown and may prove to be of importance. Selective deficiencies of the other immunoglobulins are excessively rare; in one study (Hobbs 1968)⁴ only one case was found in 11,000 hospital patients. Once case of selective IgM deficiency has been described (Stoelinga 1965)¹⁸, a male child of a consanguineous union was extensively investigated and gave a history of repeated severe infections with Gram negative bacilli and Gram positive cocci starting at the age of two, the patient's brother died in early infancy of pneumococcal meningitis and the father was found to have low IgM. This patient had steatorrhoea between the ages of five and six. Thus it should be emphasised that since selective IgA deficiency occurs asymptotically in a significant number of apparently normal people,⁴ and in association with congenital neurological disturbance in children, the role of intestinal antibodies in maintaining the integrity of structure and function of the mucosa in the small bowel and the pathogenesis of intestinal abnormalities associated with a defective immunological system involves more than the simple presence or absence of IgA. In some IgA deficient patients there is evidence that a compensating increase in IgM occurs,¹² but it is possible that there may be a qualitative defect in the other immunoglobulins and a functional compensation does not in fact take place. Indeed knowledge of such possible defects which is at present lacking might shed light on many areas of disease./

of disease.

2. The association of immunoglobulin deficiency with pernicious anaemia.

It has been found that hypogammaglobulinaemia occurs in association with certain intestinal disorders, namely pernicious anaemia and malabsorption. Nine patients have been described (Twomey 1967)⁵ one of whom is Case 3 of this series in whom a severe immunoglobulin deficiency has been established. That the deficiency has been of the adult onset type is suggested by the late onset of recurrent bacterial infections at an average age of thirty years. - the infections sustained by Case 1 began at the age of seventeen, but he has not got pernicious anaemia. Atrophic gastritis developed at an unusually early age and parietal cell antibodies were not demonstrated. The presence of allergies, rheumatoid-like arthritis and colitis in the majority of this group suggests an undue susceptibility to disorders of the immune mechanism. It seems unlikely that this association of pernicious anaemia with primary acquired hypogammaglobulinaemia is coincidental. This group of patients tended to develop atrophic gastritis at a much earlier age than is usual in pernicious anaemia, also the presence of atrophic gastritis differentiates this type of vitamin B₁₂ malabsorption from juvenile intrinsic factor deficiency. Good evidence is established from this study also that parietal cell and intrinsic factor antibodies are not essential to the development of atrophic gastritis; however it is possible that in such cases antibodies may in fact be present but existing in undetectable complexes. The presence of pernicious anaemia in patients with acquired hypogammaglobulinaemia does not imply that gastric atrophy /

atrophy cannot be mediated through immunological mechanisms; on the contrary the evidence of increased amounts of the disorders mentioned believed to have an autoimmune basis in these patients is suggestive of pernicious anaemia being an auto-immune disease. Case 1 had proven steatorrhoea and although evidence of malabsorption was not obtained in Case 3, he did have intermittent diarrhoea and as pointed out, it is quite possible that he had had malabsorption prior to investigation associated with his period of weight loss. The presence of bowel dysfunction in serum out of nine of the group of patients studied by Twomey et al is greatly in excess of the reported incidence of bowel complications in primary acquired hypogammaglobulinaemia and it seems unlikely that persistent diarrhoea can be caused by Vitamin B₁₂ depletion since bowel symptoms persisted in these patients after treatment with B₁₂. It is also unlikely that the severe immunological deficiency resulted from malabsorption of necessary constituents for gammaglobulin synthesis. The question arises therefore, whether pernicious anaemia causes immunoglobulin deficiency or vice versa? There is virtually no evidence to suggest that vitamin B₁₂ is essential for immunoglobulin synthesis, but it does seem possible that atrophic gastritis may result from repeated bacterial damage of the gastric mucosa in immunoglobulin deficient patients and although Case 1 did not have pernicious anaemia he did have histamine fast achlorhydria. The probable importance of IgA in protecting mucus membranes has been mentioned; in the nine patients studied and in Case 1 also, severe IgA deficiency existed. Selective deficiency of IgA occurs in $\frac{1}{500}$ of apparently normal people,⁴ but it is possible that in these subjects indolent infections of mucus/

mucus membranes may not have attracted attention. In Case 3 and in ~~6~~ 6 of the nine studied by Twomey et al, there was a close temporal relationship between the age at which pernicious anaemia was diagnosed and the age at which the first manifestations of immunoglobulin deficiency became apparent which suggests that a single defect may be responsible for both gastric atrophy and the immunological deficiency rather than there being a causal relationship between them and there is some evidence suggesting that the defect may be at the genetic level. ^{5, 13,}

3. Protein losing enteropathy and angioneurotic oedema; serum protein deficiencies - primary or secondary?

Recurrent episodes of intestinal colic and intestinal obstruction have been well established in patients with angioneurotic oedema and it is probable that the acute symptoms arise from gross focal involvement of the bowel wall, but it is also likely that less severe lesions causing no symptoms occur more frequently and cause loss of plasma proteins; this view is supported by the I¹³¹ - labelled albumin tumour studies carried out in case 4 from which it was shown that the hypoalbuminaemia resulted from a combination of intestinal and urinary loss - primarily the former, and a decreased hepatic synthesis. ⁷

During the three year period over which Case 4 was studied, total serum protein averaged 4.7 G/100 ml; the loss of protein from the gut was sufficient to give a serum albumin of 1.2 G/100 ml. but at no time did the serum gammaglobulin level drop below 0.7 G/100 ml; the selective loss of albumin secondary to the angioneurotic oedema lesions of the small bowel being a function of the lower molecular weight/

weight of albumin. In Case 2 a selective IgA deficiency was shown with otherwise normal serum proteins; it is unlikely that an intestinal lesion would give rise to such a specific loss, leaving other serum proteins intact. In other cases of selective IgA deficiency studied the persistence of the serum deficiency together with the same deficiency in exocrine secretions and abnormalities of the small bowel mucosa after the total serum proteins had returned to normal concentrations and faecal fat excretion had returned to normal ³ makes it unlikely that the deficiency of IgA was secondary to the malabsorption or malnutrition. The nature of the relationship between hypogammaglobulinaemia and steatorrhoea is more difficult to establish. Malabsorption has been proved in Case 1 and it is likely that it was also present in Case 3 before investigation - partial villous atrophy has been demonstrated in this case also. In other hypogammaglobulinaemia patients with proven steatorrhoea the mucosal abnormality is indistinguishable from that of idiopathic steatorrhoea, with the exception of the scarcity of plasma cells, ² and although a small number of cases, of hypogammaglobulinaemia have been described in which there has been a response to gluten withdrawal, the majority of these patients show no such response. ^{15, 16} Case 1 showed an apparent response to gluten free diet but, as he remained relatively free from bowel symptoms following its withdrawal it seems unlikely that the improvement was mediated by the absence of gluten. Specific sensitivity of wheat proteins seems to be a common phenomenon among patients suffering from adult coeliac syndromes and despite extensive studies no truly satisfactory explanation for the sensitivity has been established. It has been postulated that impaired synthesis of gammaglobulin in hypogammaglobulinaemic patients /

patients occurs secondary to reduced intestinal absorption of essential constituents due to damage to the mucosa⁽⁷⁾ but the onset of infections in some of these patients nineteen years before the development of diarrhoea and steatorrhoea suggests that the lowered gammaglobulin levels in these cases at least is the primary event and the mucosal changes might be attributed to repeated intestinal infection.^{16.}

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